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REVIEW

Cardiac Resynchronization Therapy in Heart Failure: Patients with Narrow QRS

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Heart failure remains a significant health problem in the Western countries despite the evolution achieved in terms of heart disease prevention and medical treatment. Its incidence and its prevalence reach 550,000/year and 5 million respectively in the United States. As a consequence**,** heart failure causes about 287,000 deaths in the US each year and puts a financial burden to the health system of $29.6 billion dollars due to the increasing number of hospitalizations especially in elderly patients. [1,2]

Cardiac resynchronization therapy (CRT) is a relatively recent advance in the management of heart failure patients, which has been very hopeful since its development. Large trials have established the efficacy of CRT in improving functional capacity (MUSTIC, MIRACLE) and reducing mortality (COMPANION, CARE HF) in patients with advanced heart failure (NYHA III-IV), reduced ejection fraction (EF<35%) and wide QRS complex >120 - 130 ms (MIRACLE) [3-7]. Data from meta-analyses also confirm the beneficial effect of CRT with respect to mortality from worsening heart failure and all cause mortality in patients with *wide QRS complex.* [8-10]

Nevetheless, not all patients suffering from heart failure have a prolonged QRS. On the contrary, it has been reported that nearly 50% of heart failure patients have a QRS < 120 ms. [11] Moreover, CRT has been shown to improve haemodynamic variables in patients with heart failure and narrow QRS. [12] Achilli et al, [13] who studied 52 patients, reported that CRT produced similar clinical and functional benefit in patients with wide or narrow QRS, the cut-off point being 120 ms provided they had mechanical dyssynchrony. Bleeker at al[14] came up with similar results when they compared 33 patients with normal QRS duration with an equal number of subjects with wide QRS. All participants ought to have mechanical dyssynchrony >65 ms on tissue Doppler imaging (TDI) study. Yu et al[15] confirmed these findings, showing evidence of reverse remodelling and clinical improvement in 102 patients with heart failure. Half of them demonstrated a normal width of the QRS complex and had baseline systolic dyssynchrony. Gasparini et al.[16] evaluated a total number of 376 patients with impaired systolic function and concluded that CRT was beneficial in terms of both clinical parameters and left ventricular (LV) geometry in a long-term basis, regardless of the QRS duration. Notably, the patients with a narrow QRS were not selected on the basis of mechanical dyssynchrony, but they constituted only a small percentage of the whole study population (46/376 or 12%). Another meta-analysis by Jeevanantham et al.[17] incorporating data from the studies by Yu, Bleeker and Achilli, where the patients with narrow QRS were selected on the basis of mechanical dyssynchrony, showed that there was a significant improvement in mean LVEF and six minutes walk distance (6 MWD) at the end of a follow-up period exceeding 3 months. When results from other studies with longer follow up period were included, the improvement in the former indices was even more impressive.

The ESTEEM-CRT study on the other hand, showed that patients with narrow QRS and mechanical dyssynchrony (Ts-SD-12 echocardiographic variable) did not benefit from CRT with regard to exercise tolerance and reverse remodelling. [18] Moreover, a recent study enrolling 90 patients with mechanical asynchrony regardless of their QRS width, did not find significant difference in the outcome (reduction of LVESV by 15% or more) between those with wide or narrow QRS after CRT implantation, at the end of the follow up period (1±2 months), although there was a trend for better outcome in the wide QRS arm (53 vs. 73% p=0.084). [19]

All these results however, emerge from relatively small, non-randomized studies. Subgroup analyses from larger, randomized trials may provide more reliable information. In the CARE -HF trial, those with QRS less than 160 ms did not benefit from CRT.[7] The MADIT-CRT trial which evaluated the effect of CRT-D over mere ICD implantation in patients with mild heart failure in a randomized manner, showed that resynchronization was effective in preventing new heart failure events in patients with a baseline QRS of more than 150 ms. [20] Similar results were obtained from the REVERSE trial. In this study 610 patients with NYHA class I/II heart failure, QRS duration >120 ms, LV end-diastolic dimension >55 mm, and LVEF <40% were randomized to active therapy (CRT on) or control (CRT off) for 12 months. A significant reduction in LV end-diastolic and end-systolic volume indexes and an increase in LVEF at 12 months was reported, although only for those with a baseline QRS > 140 ms.[21]

The first randomized attempt to assess the issue of CRT in narrow QRS was the RethinQ study. A total of 172 patients with a standard indication for an ICD and QRS<130 ms, were randomly assigned to receive or not a CRT device and were followed up for 6 months. In the prespecified group of resynchronised patients with normal QRS duration the primary end point of increase in O_2 consumption by at least 1.0 ml per kg of body weight per minute during cardiopulmonary exercise was not achieved, in contrast to the rest of the participants who received CRT and had a QRS wider than 120 ms.[22]

In conclusion, the concept of CRT efficacy in heart failure patients with narrow QRS is still under evaluation. The initial relatively small non-randomized trials have yielded encouraging results. However, data from larger randomized studies challenge these favourable conclusions and the RethinQ trial, the first to address this particular issue in a randomized fashion, failed to confirm the usefulness of CRT in this setting. Nevertheless, more data from large randomized trials are still needed to further elucidate this matter. A new study aiming at evaluating the effects of CRT on mortality and morbidity of subjects with heart failure due to LV systolic dysfunction, already receiving optimized medical therapy, with a narrow QRS width (< 130 ms) and echocardiographic evidence of ventricular dyssynchrony (EchoCRT) is currently recruiting patients.[23] Interesting results that will probably enlighten the field are anticipated due to the specific design and the hard endpoints of this trial.

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